Use of organophosphorus compounds for the production of pharmaceutical preparations for the therapeutic and prophylactic treatment of infections or as a fungicide, bactericide or herbicide in plants

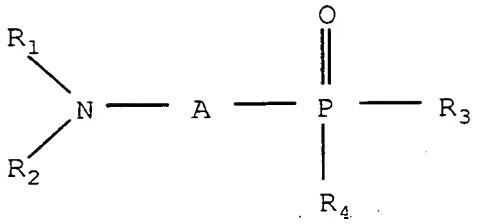
This invention relates to the use of organophosphorus compounds and the salts, esters and amides thereof for the production of pharmaceutical preparations for the therapeutic and prophylactic treatment of infections in humans and animals caused by viruses, bacteria, fungi and parasites, and to the use thereof as a fungicide, bactericide and herbicide in plants. According to the invention, the organophosphorus compounds comprise phosphinoyl derivatives and phosphinic acid derivatives.

In order to widen the range of options for treating humans and animals and for protecting plants, there is an urgent requirement to provide agents which are not only highly active but, unlike other pharmaceutical preparations or phytosanitary agents, also exhibit reduced side-effects and thus constitute a reduced risk to human health.

The object of the present invention is accordingly to provide a substance which is usable in infections by viruses, bacteria, fungi and parasites in humans and animals and as a fungicide, bactericide and herbicide in plants and which meets the above-stated requirements.

This object is utterly surprisingly achieved by the group of substances defined in claim 1. This group of substances exhibits both an antiinfective action against viruses, certain bacteria, fungi, uni- and multicellular parasites and a fungicidal, bactericidal and herbicidal action in plants.

The organophosphorus compounds used according to the invention are of the general formula (I):



(I)

in which R_1 and R_2 are identical or different and are selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue, halogen, OX_1 and OX_2,

wherein X_1 and X_2 may be identical or different and are selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue.

A is selected from the group consisting of an alkylene residue, an alkenyl residue and a hydroxyalkylene residue,

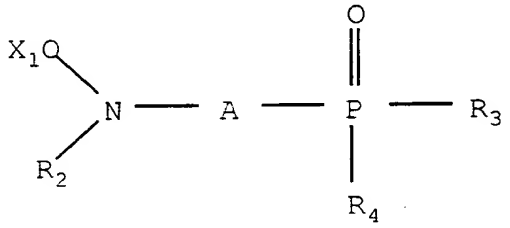
R_3 is selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, halogen,

R_4 is selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, halogen, OX_4,

wherein X_4 is selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted hydroxyalkyl, substituted and

unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted alkenyl, substituted and unsubstituted alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, a substituted or unsubstituted silyl, a cation of an organic and inorganic base, in particular of a metal of main group I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds which are derived from ethylenediamine or amino acids, and pharmaceutically acceptable salts, esters and amides and salts of the esters.

Suitable compounds are in particular those of the formula (II) below:



(II)

wherein

X_1 is selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic residue;

R_2, R_3, R_4 and A have the same meaning as in formula (I).

Particularly preferably, A is a chain of three carbon atoms which joins the nitrogen atom to the phosphorus atom. The three-membered chain may be substituted.

In particular, preferred compounds of the formula (II) are those in which R_2 = acyl, in particular a formyl or acetyl, R_3 = hydrogen, methyl or ethyl, R_4 = hydrogen, methyl, ethyl or OX_4 where X_4 = hydrogen, sodium, potassium, methyl, ethyl, X_1 = H and A = alkylene, alkenylene or hydroxyalkylene. Particularly good results are achieved with R_2 = formyl or acetyl and A = propylene, propenylene or hydroxypropylene.

Special features of the above definitions and suitable examples thereof are stated below:

"Acyl" is a substituent which originates from an acid, such as from an organic carboxylic acid, carbonic acid, carbamic acid or the thioacid or imidic acid corresponding to the individual above-stated acids, or from an organic sulfonic acid, wherein these acids may in each case comprise aliphatic, aromatic and/or heterocyclic groups in the molecule, as well as carbamoyl or carbamimidoyl.

Suitable examples of these acyl groups are stated below.

Aliphatic acyl groups are deemed to comprise acyl residues originating from an aliphatic acid, such groups including the following:
alkanoyl (for example formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl *etc.*);
alkenoyl (for example acryloyl, methacryloyl, crotonoyl *etc.*);
alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl *etc.*);
alkanesulfonyl (for example mesyl, ethanesulfonyl, propanesulfonyl *etc.*);
alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl *etc.*);
alkylcarbamoyl (for example methylcarbamoyl *etc.*);
(N-alkyl)thiocarbamoyl (for example (N-methyl)thiocarbamoyl *etc.*);
alkylcarbamimidoyl (for example methylcarbamimidoyl *etc.*);
oxalo;
alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl *etc.*).

In the above examples of aliphatic acyl groups, the aliphatic hydrocarbon moiety, in particular the alkyl group or alkane residue, may optionally comprise one or more suitable substituents, such as amino, halogen (for example fluorine, chlorine, bromine *etc.*), hydroxy, hydroxyimino, carboxy, alkoxy (for example methoxy, ethoxy, propoxy *etc.*), alkoxycarbonyl, acylamino (for example benzyloxycarbonylamino *etc.*), acyloxy (for example acetoxy, benzyloxy *etc.*) and the like; preferred aliphatic acyl residues having such substituents which may be mentioned are alkanoyls

substituted, for example, with amino, carboxy, amino and carboxy, halogen, acylamino or the like.

Aromatic acyl residues are deemed to comprise those acyl residue which originate from an acid with a substituted or unsubstituted aryl group, wherein the aryl group may comprise phenyl, toluyl, xylyl, naphthyl and the like; suitable examples are stated below:

aroyl (for example benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl *etc.*);

aralkanoyl (for example phenylacetyl *etc.*);

aralkenoyl (for example cinnamoyl *etc.*);

aryloxyalkanoyl (for example phenoxyacetyl *etc.*);

arylthioalkanoyl (for example phenylthioacetyl *etc.*);

arylaminoalkanoyl (for example N-phenylglycyl *etc.*);

arenesulfonyl (for example benzenesulfonyl, tosyl or toluenesulfonyl, naphthalene-sulfonyl *etc.*);

aryloxycarbonyl (for example phenoxycarbonyl, naphthyloxycarbonyl *etc.*);

aralkoxycarbonyl (for example benzyloxycarbonyl *etc.*);

arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl *etc.*);

arylglyoxyloyl (for example phenylglyoxyloyl *etc.*).

In the above examples of acyl residues, the aromatic hydrocarbon moiety (in particular the aryl residue) and/or the aliphatic hydrocarbon moiety (in particular the alkane residue) may optionally comprise one or more suitable substituents, such as those which have already been stated as suitable substituents for the alkyl group or the alkane residue. Aromatic acyl residues having particular substituents which may in particular be mentioned and constitute examples of preferred aromatic acyl residues are aroyl substituted with halogen and hydroxy or with halogen and acyloxy, and aralkanoyl substituted with hydroxy, hydroxyimino, dihaloalkanoyloxyimino, together with arylthiocarbamoyl (for example phenylthiocarbamoyl *etc.*);

arylcarbamimidoyl (for example phenylcarbamimidoyl *etc.*).

A heterocyclic acyl residue is taken to mean an acyl residue which originates from an acid with a heterocyclic group; these include:

heterocyclic carbonyl, in which the heterocyclic residue is an aromatic or aliphatic 5- to 6-membered heterocycle with at least one heteroatom from the group comprising nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolocarbonyl, nicotinoyl *etc.*);

alkanoyl heterocycle, in which the heterocyclic residue is 5- to 6-membered and comprises at least one heteroatom from the group comprising nitrogen, oxygen and sulfur (for example thiophenylacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl *etc.*) and the like.

In the above examples of heterocyclic acyl residues, the heterocycle and/or the aliphatic hydrocarbon moiety may optionally comprise one or more suitable substituents, such as those as have been stated to be suitable for alkyl and alkane groups.

"Alkyl" is a straight- or branched-chain alkyl residue with up to 9 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and the like.

"Hydroxyalkyl" is a straight- or branched-chain alkyl residue with up to 9 carbon atoms which comprises at least one hydroxyl group, preferably one or two hydroxyl groups.

"Alkenyl" includes straight- or branched-chain alkenyl groups with up to 9 carbon atoms, such as for example vinyl, propenyl (for example 1-propenyl, 2-propenyl), 1-methylpropenyl, 2-methylpropenyl, butenyl, 2-ethylpropenyl, pentenyl, hexenyl.

"Alkynyl" includes linear- or branched-chain alkynyl groups with up to 9 carbon atoms.

Cycloalkyl preferably denotes an optionally substituted C3-C7 cycloalkyl; possibly suitable substituents are *inter alia* alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy *etc.*), halogen (for example fluorine, chlorine, bromine *etc.*), nitro and the like.

Aryl is an aromatic hydrocarbon residue, such as phenyl, naphthyl *etc.*, which may optionally comprise one or more suitable substituents, such as alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy *etc.*), halogen (for example fluorine, chlorine, bromine *etc.*), nitro and the like.

"Aralkyl" includes mono-, di- and triphenylalkyls, such as benzyl, phenethyl, benzhydryl, trityl and the like, wherein the aromatic moiety may optionally comprise one or more suitable substituents, such as alkoxy (for example methoxy, ethoxy *etc.*), halogen (for example fluorine, chlorine, bromine *etc.*), nitro and the like.

"Alkylene" includes straight- or branched-chain alkylene groups which comprise up to 9 carbon atoms and may be represented by the formula

$$-(C_nH_{2n})-$$

in which n is an integer from 1 to 9, such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, 1-methyltrimethylene, 2-ethylethylene, pentamethylene, 2-methyltetramethylene, isopropylethylene, hexamethylene and the like; preferred alkylene residues have up to 4 carbon atoms and particularly preferred residues are those with 3 carbon atoms, such as for example trimethylene. The hydrogen atoms may be replaced by other substituents, such as for example halogen residues.

"Alkenylene" includes straight- or branched-chain alkenylene groups with up to 9 carbon atoms, which may be represented by the formula

$-(C_nH_{2n-2})-$

in which n is an integer from 2 to 9, such as for example vinylene, propenylene (for example 1-propenylene, 2-propenylene), 1-methylpropenylene, 2-methylpropenylene, butenylene, 2-ethylpropenylene, pentenylene, hexenylene and the like; the alkenylene residue may particularly preferably comprise up to 5 carbon atoms and, in particular, 3 carbon atoms, such as for example 1-propenylene. The hydrogen atoms may be replaced by other substituents, such as for example halogen residues.

"Hydroxyalkylene" may include straight- or branched-chain alkylene residues which comprise up to 9 carbon atoms, wherein at least one selected carbon atom is substituted with a hydroxy group; these residues may be represented by the formula

$-(C_nH_{2n-z})(OH)_z-$

in which n is an integer from 1 to 9 and z is an integer to which the relation $1 \leq z \leq n$ applies. Suitable examples of such hydroxyalkylene groups include hydroxymethylene, hydroxyethylene (for example 1-hydroxyethylene and 2-hydroxyethylene), hydroxytrimethylene (for example 1-hydroxytrimethylene, 2-hydroxytrimethylene and 3-hydroxytrimethylene), hydroxytetramethylene (for example 2-hydroxytetramethylene), 2-hydroxy-2-methyltrimethylene, hydroxypentamethylene (for example 2-hydroxypentamethylene), hydroxyhexamethylene (for example 2-hydroxyhexamethylene) and the like. A lower hydroxyalkylene comprising up to 4 carbon atoms is particularly preferred and in particular such a compound comprising 3 carbon atoms, such as for example 2-hydroxytrimethylene. The hydrogen atoms may be replaced by other substituents, such as for example halogen residues.

The residue X_4 may preferably be selected such that esters are formed on the phosphino group. Suitable examples of such esters of the formulae (I) and (II) include alkyl esters (for example methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, isobutyl esters, hexyl esters *etc.*);

aralkyl esters (benzyl esters, phenylethyl esters, benzhydryl esters, trityl esters *etc.*);

aryl esters (for example phenyl esters, tolyl esters, naphthyl esters *etc.*); aroylalkyl esters (for example phenacyl esters *etc.*); and silyl esters (for example of trialkylhalosilyl, dialkyldihalosilyl, alkyltrihalosilyl, dialkylarylhalosilyl, trialkoxyhalosilyl, dialkylaralkylhalosilyl, dialkoxydihalosilyl, trialkoxyhalosilyl *etc.*) and the like.

In the above esters, the alkane and/or arene moiety may optionally comprise at least one suitable substituent, such as halogen, alkoxy, hydroxy, nitro or the like.

X_4 is preferably a metal of main group I, II or III of the periodic system, ammonium, substituted ammonium or ammonium compounds which are derived from ethylenediamine or amino acids. In other words, the salt compounds of the organophosphorus compounds are formed with organic or inorganic bases (for example sodium salt, potassium salt, calcium salt, aluminium salt, ammonium salt, magnesium salt, triethylamine salt, ethanolamine salt, dicyclohexylamine salt, ethylenediamine salt, N,N'-dibenzylethylenediamine salt *etc.*) as are salts with amino acids (for example arginine salt, aspartic acid salt, glutamic acid salt *etc.*) and the like.

The compounds of the formula (I) or (II) used according to the invention may assume the protonated form thereof as an ammonium salt of organic or inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, acetic acid, lactic acid, maleic acid, fumaric acid, oxalic acid, tartaric acid, benzoic acid *etc.*.

The compounds of the formula (I) or (II) used according to the invention permit the occurrence spatial isomers, for example for double bond-containing or chiral groups R_1, R_2, R_3, R_4, X_1, X_2, X_4 or A. The use according to the invention of the compounds includes all spatial isomers, both as pure substances and in the form of mixtures thereof.

The organophosphorus compounds are in particular suitable for the therapeutic and prophylactic treatment of human and animal infections which are caused by viruses, bacteria, uni- and multicellular parasites and fungi.

The compounds are active against unicellular parasites (protozoa), in particular against the causative organisms of malaria and sleeping sickness and of Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

They are accordingly in particular suitable for the prophylactic treatment of malaria and of sleeping sickness and of Chagas' disease, of toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

The active substances according to the invention may in particular be used against the following bacteria:

bacteria of the family *Propionibacteriaceae*, in particular of the genus *Propionibacterium*, in particular the species *Propionibacterium acnes*, bacteria of the family *Actinomycetaceae*, in particular of the genus *Actinomyces*, bacteria of the genus *Cornynebacterium*, in particular the species *Corynebacterium diphtheriae* and *Corynebacterium pseudotuberculosis*, bacteria of the family *Mycobacteriaceae*, of the genus *Mycobacterium*, in particular the species *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycobacterium bovis* and *Mycobacterium avium*, bacteria of the family *Chlamydiaceae*, in particular the species *Chlamydia trachomatis* and *Chlamydia psittaci*, bacteria of the genus *Listeria*, in particular the species *Listeria monocytogenes*, bacteria of the species *Erysipelthrix rhusiopathiae*, bacteria of the genus *Clostridium*, bacteria of the genus *Yersinia*, the species *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia enterocolitica* and *Yersinia ruckeri*, bacteria of the family *Mycoplasmataceae*, of the genera *Mycoplasma* and *Ureaplasma*, in particular the species *Mycoplasma pneumoniae*, bacteria of the genus

Brucella, bacteria of the genus *Bordetella*, bacteria of the genus *Campylobacter*, in particular the species *Campylobacter jejuni*, *Campylobacter coli* and *Campylobacter fetus*, bacteria of the genus *Helicobacter*, in particular the species *Helicobacter pylori*, bacteria of the families *Spirochaetaceae* and *Leptospiraceae*, in particular the genera *Treponema*, *Borrelia* and *Leptospira*, in particular *Borrelia burgdorferi*, bacteria of the genus *Actinobacillus*, bacteria of the family *Legionellaceae*, of the genus *Legionella*, bacteria of the family *Rickettsiaceae* and the family *Bartonellaceae*, bacteria of the genera *Nocardia* and *Rhodococcus* and bacteria of the genus *Dermatophilus*.

Organophosphorus compounds and the derivatives thereof are consequently suitable for treating diphtheria, acne vulgaris, listerioses, swine erysipelas in animals, gas gangrene in humans and animals, malignant oedema in humans and animals, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, plague, mesenterial lymphadenitis and pseudotuberculosis in humans and animals, cholera, legionnaires' disease, borreliosis in humans and animals, leptospiroses in humans and animals, syphilis, *Campylobacter* enteritis infections in humans and animals, *Moraxella* keratoconjunctivitis and serositis in animals, brucellosis of animals and humans, anthrax in humans and animals, actinomycosis in humans and animals, streptotrichoses, psittacosis/ortnithosis in animals, Q fever, ehrlichiosis.

Use is furthermore effective in the eradication of *Helicobacter* in ulcers of the gastrointestinal tract.

Combinations with another antibiotic may also be used to treat the above-stated diseases. Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and dapsone are in particular suitable for combination preparations with other antiinfective agents for the treatment of tuberculosis.

The active substances according to the invention are furthermore usable in infections with the following viruses:

Parvoviridae: parvoviruses, dependoviruses, densoviruses, *Adenoviridae*: adenoviruses, mastadenoviruses, aviadenoviruses, *Papovaviridae*: papovaviruses, in particular papillomaviruses ("wart" viruses), polyomaviruses, in particular JC virus, BK virus and miopapovaviruses, *Herpesviridae*: all herpesviruses, in particular herpes simplex viruses, varicella-zoster viruses, human cytomegalovirus, Epstein-Barr viruses, all human herpesviruses, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8, *Poxiviridae*: poxviruses, orthopoxviruses, parapoxviruses, molluscum contagiosum virus, aviviruses, capriviruses, leporipoxviruses, all primarily hepatotropic viruses, hepatitisviruses: hepatitis A viruses, hepatitis B viruses, hepatitis C viruses, hepatitis D viruses, hepatitis E viruses, hepatitis F viruses, hepatitis G viruses, hepadnaviruses: all hepatitisviruses, hepatitis B virus, hepatitis D viruses, *Picornaviridae*: picornaviruses, all enteroviruses, all polioviruses, all coxsackie-viruses, all echoviruses. all rhinoviruses, hepatitis A virus, aphthoviruses, *Calciviridae*: hepatitis E viruses, *Reoviridae*: reoviruses, orbiviruses, rotaviruses, *Togaviridae*: togaviruses, alphaviruses, rubiviruses, pestiviruses, rubellavirus, *Flaviviridae*: flaviviruses. FSME virus, hepatitis C virus, *Orthomyxoviridae*: all influenza viruses, *Paramyxoviridae*: paramyxoviruses, morbillivirus, pneumovirus, measles virus, mumps virus, *Rhabdoviridae*: rhabdoviruses, rabies virus, lyssavirus, vascular stomatitisvirus. *Coronaviridae*: coronaviruses, *Bunyaviridae*: bunyaviruses, nairovirus, phlebovirus, uukuvirus, hantavirus, hantaan virus, *Arenaviridae*: arenaviruses, lymphocytic choriomeningitis virus, *Retroviridae*: retroviruses, all HTL viruses, human T-cell leukaemia virus, oncornaviruses, spumaviruses, lentiviruses, all HI viruses. *Filoviridae*: Marburg and Ebola virus, slow-virus infections, prions, oncoviruses and leukaemia viruses.

The organophosphorus compounds used according to the invention are consequently suitable for combating the following viral infections:

eradication of papillomaviruses to prevent tumours, in particular tumours of the reproductive organs caused by papillomaviruses in humans, eradication of JC viruses and BK viruses, eradication of herpesviruses, eradication of human herpesvirus 8 to treat Kaposi's sarcoma, eradication of cytomegaloviruses before transplantations,

eradication of Epstein-Barr viruses before transplantation and to prevent tumours associated with Epstein-Barr viruses, eradication of hepatitis viruses to treat chronic liver disease and to prevent liver tumours and cirrhosis of the liver, eradication of coxsackieviruses in cardiomyopathy, eradication of coxsackieviruses in diabetes mellitus patients, eradication of immunodeficiency viruses in humans and animals, treatment of accompanying infections in AIDS patients, treatment of respiratory tract inflammation of viral causation (laryngeal papilloma, hyperplasia, rhinitis, pharyngitis, bronchitis, pneumonia), of the sensory organs (keratoconjunctivitis), of the nervous system (poliomyelitis, meningoencephalitis, encephalitis, subacute sclerosing panencephalitis, SSPE, progressive multifocal leukoencephalopathy, lymphocytic choriomeningitis), of the gastrointestinal tract (stomatitis, gingivostomatitis, oesophagitis, gastritis, gastroenteritis, diarrhoea), of the liver and gall system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haemopoietic system, of the reproductive organs (mumps orchitis), of the skin (warts, dermatitis, herpes labialis, herpes febrilis, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctival papillomas, hyperplasia, dysplasia), of the cardiovascular system (arteriitis, myocarditis, endocarditis, pericarditis), of the kidney/urinary system, of the reproductive organs (anogenital lesions, warts, genital warts, sharp condylomas, dysplasia, papillomas, cervical dysplasia, condyloma acuminatum, epidermodysplasia verruciformis), of the locomotory organs (myositis, myalgia), treatment of foot-and-mouth disease in cloven-hoofed animals, of Colorado tick fever, Dengue syndrome, of haemorrhagic fever, of early summer meningoencephalitis (FSME) and of yellow fever.

The described compounds, *i.e.* the organophosphorus compounds of the formula (I) and (II) and esters and amides thereof on the phosphino group and salts thereof exhibit strong cytotoxic activity against uni- and multicellular parasites, in particular against the causative organisms of malaria and sleeping sickness. The compounds used according to the invention are accordingly usable for the treatment of infective diseases which are caused in humans and animals by viruses, bacteria, parasites and fungi. The compounds are also suitable for the prevention of diseases which are

caused by viruses, bacteria, parasites and fungi, in particular for the prophylactic treatment of malaria and of sleeping sickness.

The organophosphorus compounds used according to the invention, which generally include for this purpose pharmaceutically acceptable salts, amides, esters, a salt of such an ester or also compounds which, on administration, provide the compounds used according to the invention as metabolites or breakdown products (also known as "prodrugs"), may be formulated for administration in any suitable manner analogous to known agents having an antiinfective action (mixed with a non-toxic, pharmaceutically acceptable excipient).

Pharmaceutically acceptable salts of the compounds include salts which the compounds of the formulae (I) and (II) used according to the invention form in their protonated form as an ammonium salt of inorganic or organic acids, such as hydrochloric acid, sulfuric acid, citric acid, maleic acid, fumaric acid, tartaric acid, p-toluenesulfonic acid.

Particularly pharmaceutically suitable salts are also those formed by suitable selection of X_4, such as sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt, triethylamine salt, dicyclohexylamine salt and salts of an amino acid such as arginine salt, aspartic acid salt, glutamic acid salt.

Use of the above-stated substances is in particular suitable for the production of pharmaceutical preparations against bacterial diseases or for the prevention thereof or for the production of herbicides.

The activity of the substances is determined using a test system. This system is based upon *in vitro* measurement of the inhibition of growth of bacteria, parasites, viruses, fungi or plants. Test methods known to the person skilled in the art are in part used for this purpose.

For example, antimalarial activity is determined by measuring the inhibition of the growth of malaria parasites in blood cultures.

Antibacterial activity is determined on the basis of measuring the inhibition of bacterial growth on nutrient media and in liquid cultures.

Antiviral activity is determined on the basis of the formation of viral elements in cell cultures.

Some of the microorganisms which are to be investigated may only be investigated in animal models. In this case, we will then use the appropriate models.

Substances which exhibit activity in *in vitro* measurement systems are then further investigated in *in vivo* models.
The antiparasitic, antiviral, fungicidal or antibacterial activity is further evaluated in the appropriate animal models.

Screening for herbicidal activity is determined by means of algal systems and measurement of isoprene emissions from plants under standard conditions.

The pharmaceutically active agents may be prepared in dosage units in the form of pharmaceutical preparations. This means that the preparation is in the form of individual components, for example tablets, coated tablets, capsules, pills, suppositories and ampoules, the active substance content of which corresponds to a fraction or multiple of an individual dose. The dosage units may contain, for example 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the quantity of active substance which is administered at one time and usually corresponds to a whole, half, third or quarter of a daily dose.

Non-toxic, inert, pharmaceutically suitable excipients should be taken to mean solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all kinds.

Preferred pharmaceutical preparations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, coated tablets, capsules, pills and granules may contains the active substances together with conventional excipients, such as (a) fillers and extenders, for example starches, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxy-methylcellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, coated tablets, capsules, pills and granules may be provided with conventional coatings and shells optionally containing opacifying agents and may also be composed such that they release the active substances only with a delay or preferably in a particular part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as the matrices.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also be present in microencapsulated form.

In addition to the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa butter and higher esters (for example C14 alcohol with C16 fatty acid) or mixtures of these substances.

In addition to the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes,

paraffins, starch, gum tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

In addition to the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluorocarbons.

In addition to the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

For parenteral administration, the solutions and emulsions may also be present in sterile, isotonic form.

In addition to the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and gum tragacanth or mixtures of these substances.

The stated formulations may also contain colorants, preservatives and odour- or flavour-enhancing additives, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The active substances of the formulae (I) and (II) should preferably be present in the pharmaceutical preparations listed above in a concentration of approx. 0.1 to 99.5 wt.%, preferably from approx. 0.5 to 95 wt.%, of the complete mixture.

Apart from the compounds of the formulae (I) and (II), the pharmaceutical preparations may also contain further pharmaceutical active substances.

The compounds may be used together with hitherto described substances having antibacterial, antiviral, antimycotic and antiparasitic properties. Such substances in particular include compounds which have already been used in therapeutic applications or are still used. Substances which are suitable for this purpose are in particular those listed in the Red List or in Simon/Stille, *Antibiokia-Therapie in Klinik und Praxis*, 9th edition, 1998, Schatauer Verlag, or on the Internet at http://www.customs.treas.gov/imp-exp/rulings/harmoniz/hrm129.html. The derivatives may in particular be present with penicillins. benzylpenicillin (penicillin G), phenoxypenicillins, isoxazolylpenicillins, aminopenicillins, ampicillin, amoxicillin, bacampicillin, carboxypenicillin, ticarcillin, temocillin, acylaminopenicillins, azlocillin, mezlocillin, piperacillin, apalcillin, mecillinam, cephalosporins, cefazolin group, cefuroxime group, cefoxitin group, cefoxitin, cefotetan, cefmetazole, latamoxef, flomoxef, cefotaxime group, cefozidime, ceftazidime group, ceftazidime, cefpirome, cefepime, conventional cephalosporins, cefsulodin, cefoperazone, oral cephalosporins of the cephalexin group, loracarbef, cefprozil, new broad-spectrum oral cephalosporins, cefixime, cefpodoxime-proxetil, cefuroxime-axetil, cefetamet, cefotiam-hexetil, cefdinir, ceftibuten, other β-lactam antibiotics, carbapenem, imipenem/cilastatin, meropenem, biapenem, aztreonam, β-lactamase inhibitors, clavulanic acid/amoxicillin, clavulanic acid/ticarcillin, sulbactam/ampicillin, tazobactam/piperacillin, tetracyclines, oxytetracycline, rolitetracycline, doxycycline, minocycline, chloramphenicol, aminoglycosides, gentamicin, tobramycin, netilmicin, amikacin, spectinomycin, macrolides, erythromycin, clarithromycin, roxithromycin, azithromycin, dirithromycin, spiramycin, josamycin, lincosamides, clindamycin, fusidic acid, glycopeptide antibiotics, vancomycin, teicoplanin, pristinamycin derivatives, fosfomycin, antimicrobial folic acid antagonists, sulfonamides,

co-trimoxazole, trimethoprim, other diaminopyrimidine-sulfonamide combinations, nitrofurans, nitrofurantoin, nitrofurazone, gyrase inhibitors (quinolones), norfloxacin, ciprofloxacin, ofloxacin, sparfloxacin, enoxacin, fleroxacin, pefloxacin, lomefloxacin, Bay Y3118, nitroimidazoles, antimycobacterial agents, isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, streptomycin, capreomycin, prothionamide, terizidone, dapsone, clofazimine, topical antibiotics, bacitracin, tyrothricin, polymyxins, neomycin, kanamycin, paromomycin, mupirocin, antiviral agents, acyclovir, ganciclovir, azidothymidine, didanosine, zalcitabine, thiacytidine, stavudine, ribavirin, idoxuridine, trifluridine, foscarnet, amantadine, interferons, tibol derivatives, proteinase inhibitors, antimycotics, polyenes, amphotericin B, nystatin, natamycin, azoles, azoles for septic therapy, miconazole, ketoconazole, itraconazole, fluconazole, UK-109,496, azoles for topical use, clotrimazole, econazole, isoconazole, oxiconazole, bifonazole, flucytosine, griseofulvin, ciclopirox olamine, tolnafnate, naftifine, terbinafine, amorolfine, anthraquinones, betulinic acid, semianthraquinones, xanthones, naphthoquinones, arylamino alcohols, quinine, quinidines, mefloquine, halofantrine, chloroquine, amodiaquine, acridine, benzonaphthyridine, mepacrine, pyronaridine, dapsone, sulfonamides, sulfadoxine, sulfalenes, trimethoprim, proguanil, chlorproguanil, diaminopyrimidines, pyrimethamine, primaquine, aminoquinolines, WR 238,605, tetracycline, doxycycline, clindamycin, norfloxacin, ciprofloxacin, ofloxacin, artemisinin, dihydroartemisinin, 10b artemether, arteether, atresunate, atovaquone, suramin, melarsoprol, nifurtimox, stibogluconate sodium, pentamidine, amphotericin B, metronidazole, clioquinol, mebendazole, niclosamide, praziquantel, pyrantel, tiabenzazole, diethylcarbamazine, ivermectin, bithionol, oxamniquine, metrifonate, piperazine, embonate.

The organophosphorus compounds may furthermore be present in the pharmaceutical preparations in combination with sulfonamide, sulfadoxine, artemisinin, atovaquone, quinine, chloroquine, hydroxychloroquine, mefloquine, halofantrine, pyrimethamine, armesin, tetracyclines, doxycycline, proguanil, metronidazole, praziquantel, niclosamide, mebendazole, pyrantel, tiabendazole, diethylcarbazine, piperazine, pyrivinium, metrifonate, oxamniquine, bithionol or suramin or two or more of these substances.

The above-stated pharmaceutical preparations are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans and animals orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, topically (powders, ointments, drops) and for the treatment of infections in cavities, body cavities. Suitable preparations which may be considered are solutions for injections, solutions and suspensions for oral therapy, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. Administration to animals may also be achieved via the feed or drinking water in suitable formulations. Gels, pulverulent formulations. powders, tablets, controlled-release tablets, premixes, concentrates, granules, pellets, tablets, boli, capsules, aerosols, sprays, inhalation formulations may also be used in humans and animals. The compounds used according to the invention may also be incorporated into other supports, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

It has in general proved advantageous in both human and veterinary medicine to administer the active substances of the formulae (I) and (II) in total quantities of approx. 0.05 to approx. 600, preferably of 0.5 to 200 mg/kg body weight per 24 hours, optionally in the form of two or more individual doses in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 1 to approx. 200, in particular of 1 to 60 mg/kg body weight. It may, however, be necessary to deviate from the stated dosages, in particular as a function of the nature and body weight of the patient to be treated, the nature and severity of the disease, the nature of the preparations and the route of administration of the drug and the period of time over which administration is performed.

In some cases, it may be sufficient to use less than the above-stated quantity of active substance, while in other cases more than the above-stated quantity of active substance must be used. The person skilled in the art will use his/her skill to determine the optimum dosage and route of administration required in each particular case.

The compounds according to the invention may be given to animals in conventional concentrations and preparations together with feed or feed preparations or with drinking water.

The compounds used according to the invention are furthermore ideally usable as bactericides, fungicides and herbicides in plants.